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Prescriber Compliance With Liver Monitoring Guidelines for Pazopanib in the Postapproval Setting: Results From a Distributed Research Network

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Objectives: Pazopanib received US Food and Drug Administration approval in 2009 for advanced renal cell carcinoma. During clinical development, liver chemistry abnormalities and adverse hepatic events were observed, leading to a boxed warning for hepatotoxicity and detailed label prescriber guidelines for liver monitoring. As part of postapproval regulatory commitments, a cohort study was conducted to assess prescriber compliance with liver monitoring guidelines.

Methods: Over a 4-year period, a distributed network approach was used across 3 databases: US Veterans Affairs Healthcare System, a US outpatient oncology community practice database, and the Dutch PHARMO Database Network. Measures of prescriber compliance were designed using the original pazopanib label guidelines for liver monitoring.

Results: Results from the VA (n = 288) and oncology databases (n = 283) indicate that prescriber liver chemistry monitoring was less than 100%: 73% to 74% compliance with baseline testing and 37% to 39% compliance with testing every 4 weeks. Compliance was highest near drug initiation and decreased over time. Among patients who should have had weekly testing, the compliance was 56% in both databases. The more serious elevations examined, including combinations of liver enzyme elevations meeting the laboratory definition of Hy's law were infrequent but always led to appropriate discontinuation of pazopanib. Only 4 patients were identified for analysis in the Dutch database; none had recorded baseline testing.

Conclusions: In this population-based study, prescriber compliance was reasonable near pazopanib initiation but low during subsequent weeks of treatment. This study provides information from real-world community practice settings and offers feedback to regulators on the effectiveness of label monitoring guidelines.

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Pazopanib is a tyrosine kinase inhibitor (TKI) that was approved as an oral targeted therapy for advanced renal cell carcinoma (RCC) by the US Food and Drug Administration in 2009 and the European Medicines Agency in 2010. Hepatotoxicity was observed during clinical development and the pivotal phase 3 clinical trial conducted among advanced or metastatic RCC patients.[1] As a result, the label information contains a boxed warning regarding hepatotoxicity along with prescriber guidelines for liver monitoring.[2] These guidelines stipulated liver chemistry (LC) tests to be performed before drug initiation and every 4 weeks for the first 4 months of treatment, along with instructions for monitoring following LC elevations. In February 2013, these guidelines were revised, requiring more frequent liver monitoring during the first several weeks of pazopanib use.[3] This change was the result of periodic safety reviews of pazopanib clinical trial data, showing that the majority of elevated liver chemistries occurred within the first 2 months of drug initiation.[3]

As part of postapproval regulatory commitments, parallel epidemiologic analyses were conducted in multiple electronic medical record (EMR) databases to characterize prescriber compliance with pazopanib liver safety monitoring guidelines among RCC patients. Sequential semiannual retrospective analyses on prospectively accrued data tracked compliance with the original label guidelines, before the 2013 revision, and during the first 4 years of pazopanib's availability in the United States.

METHODS

Data Sources

A distributed research network was used for this study. Specifically, an epidemiologic cohort study was implemented within 3 EMR databases: Altos, US Veterans Affairs Healthcare System (VA), and PHARMO. Altos contains EMR data for more than 400,000 cancer patients seen in 150 outpatient oncology practices serving more than 1000 clinicians across the United States. For each patient visit, data include diagnoses and treatment prescribed by or administered in the oncology clinic. Clinical laboratory results are available through an automated link. The VA is a national, integrated health-care system with longitudinal data for more than 12 million veterans during the most complete era of electronic data capture. Data regarding inpatient and outpatient encounters, procedures, inpatient and outpatient medications, and up to 60 selected laboratories are available spanning 10 years. In addition, all-cause mortality is available for all veterans, with cause-specific mortality available for selected states.

The Dutch-based PHARMO Institute has access to the PHARMO Database Network, a population-based network of

health-care databases that combines data from different health-care settings in the Netherlands. Data sources include general practitioner, in- and out-patient pharmacy, clinical laboratory, hospitals, cancer registry, pathology registry, and perinatal registry. Detailed information on the methodology and validation of the record linkage methods can be found elsewhere.[4,5]

Cohort Selection

A surveillance common protocol was developed and implemented by a central coordinating center to ensure consistent patient eligibility, selection criteria, and methodology across administrative databases. Within each database, new adult (18+ years) users of pazopanib with a diagnosis of RCC were identified from the earliest date of pazopanib availability in the system after FDA approval in October 2009 through February 17, 2013 (6 weeks before the study end date, March 31, 2013). New pazopanib use was defined as the first prescription recorded in the database (index date). Because many patients beginning cancer treatment are new to the oncology practice, no minimum duration of baseline enrollment was required. To minimize the likelihood that patients missing all laboratory data due to nonlinkage were not inadvertently included (with results subsequently biased toward noncompliance), an additional requirement of having at least one laboratory test, not necessarily a liver enzyme test, in the 12 months before the index date was required. Use of other chemotherapy agents concurrently with pazopanib was permitted.

Pazopanib Exposure

Dates of pazopanib exposure were derived from prescription records; when treatment duration was not specified, we assigned a duration to each order of 30 days. A continuous course of treatment was defined as sequential prescriptions for pazopanib, including all refills indicated in the prescription, separated by gaps of no more than 30 days. A gap of greater than this duration flagged the end of one course of therapy and the start of a new treatment episode. Initiation of an alternate treatment for RCC that would not be expected to be used in combination with pazopanib, with no repeat prescription of pazopanib after the start of the new treatment, was also used as an indicator of the end of a pazopanib episode.

Baseline Variables

The following patient demographic, medical, and treatment characteristics were identified using electronic data: RCC type (ICD-9 codes 189.0 or 189.1); age; gender; number of pazopanib prescription orders; comorbidities (ICD-9 codes): hepatitis B (070.2x, 070.3x), hepatitis C (070.41, 070.44, 070.51, 070.54, 070.7x), diabetes (249.xx, 250.xx), alcoholism (303.xx), steatohepatitis (alcoholic (571.0) or nonalcoholic (571.8)), autoimmune hepatitis (571.42), cholestatic liver disorders (571.6, 576.2), HIV (042, V08), obesity (278.00, 278.01, or BMI ≥ 30), liver metastases (197.7), secondary tumors (196.xx-198.xx); concomitant medications (drugs ordered or administered within 30 days before index date or during pazopanib exposure); chemotherapy agents (before the index date); and line of treatment for the qualifying index regimen (defined from all available information on chemotherapy exposure preceding pazopanib).

Measures of Compliance

Specific measures of pazopanib prescriber compliance with liver monitoring guidelines were designed from the pazopanib label guidelines. The following 3 measures were created to assess the guideline directive, "Monitor serum liver test before initiation of treatment and at least once every four weeks for at least the first four months or as clinically directed."

1) Baseline LC monitoring: compliance was measured as having both an alanine aminotransferase (ALT) and a bilirubin test on the index date or within the previous 30 days.
2) LC monitoring every 4 weeks for 4 months: For this measure, only patients with baseline LCs within normal limits and continuous use of pazopanib for 18 weeks were examined. Compliance was defined as having both ALT and bilirubin tests at every 4-week interval after the index date, where the 4-week intervals included the 2 weeks before and after each 4-week point (eg, for the first interval, a patient needed an ALT and bilirubin test between 2 and 6 weeks after the index date).
3) LC monitoring every 4 weeks for up to 4 months: This measure did not require continuous pazopanib use for 18 weeks. Patients with shorter durations of pazopanib use were considered compliant if they had received ALT and bilirubin testing during each 4-week interval that they completed, including the baseline period. For example, a patient with 6 weeks of pazopanib exposure was required to have one ALT and bilirubin test during weeks 2 to 6 to qualify as compliant. For patients with less than a 6-week course of pazopanib, the baseline LCs were considered sufficient to show compliance, as they had not yet had the full 42 days allowed for the assessment of compliance at the 4-week time point.

The label guidelines also stipulate monitoring for patients with various degrees of LC elevations during pazopanib use. The first such directive states: "Patients with isolated ALT elevations between 3x upper limit of normal (ULN) and 8xULN may be continued on pazopanib with weekly monitoring of liver function until ALT returns to grade 1 or baseline." Compliance was measured through a combination of frequency of LC monitoring and LC levels. Patients included in this analysis were those with a baseline LC at any level and with an isolated ALT elevation of 3 to 8xULN during the first continuous course of pazopanib use who remained on pazopanib after the elevation. Weekly LC monitoring, with a grace period of 3 days to either side of each weekly time point, was examined for the duration of pazopanib use, ending at the earlier of a return of ALT to baseline or no more than 2.5xULN (grade 1) or pazopanib discontinuation.

To assess compliance with the guideline stating: "Patients with isolated ALT elevations of >8xULN should have pazopanib interrupted until they return to grade 1 or baseline," patients with a baseline LC at any level and an isolated ALT elevation greater than 8xULN during the first course of pazopanib were followed to check for the absence of pazopanib use until ALT returned to baseline or no more than 2.5xULN.

For the guideline indicating that "If ALT elevations >3xULN occur concurrently with bilirubin elevations >2xULN, pazopanib should be permanently discontinued," patients with this combination of elevations during the first course of pazopanib, who also had a baseline LC at any level, were followed to check for any further pazopanib prescriptions during all available follow-up time. Compliance required no further pazopanib prescriptions at any time after the elevation.

Finally, prescribing guidelines direct prescribers not to use the drug in those with pre-existing severe hepatic impairment: "The safety of pazopanib in patients with pre-existing severe hepatic impairment, defined as total bilirubin >3xULN with any level of ALT is unknown. Treatment with pazopanib…is not recommended." Compliance with this guideline was defined as having total bilirubin of 3xULN or lesser at baseline. Eligible patients were those with any baseline LC.

Analysis

All analyses were conducted separately for each database. Data were extracted and analyzed at 6-month intervals during

TABLE 1. Characteristics of Pazopanib Initiators in the Altos and Veterans Affairs Databases

Patient Characteristic	Altos (n = 283) n (%)	VA (n = 288) n (%)
Age at pazopanib initiation, yr		
Mean (standard deviation)	65.1 (10.6)	68.1 (8.7)
Sex		
Male	191 (67.5)	283 (98.3)
Female	92 (32.5)	5 (1.7)
Sites of metastases (ICD-9 code)		
Lymph nodes of head, face, neck (196.0)	2 (0.7)	4 (1.4)
Intra-abdominal lymph nodes (196.2)	1 (0.4)	22 (7.6)
Lymph nodes lower limb (196.5)	0 (0)	1 (0.3)
Intrapelvic lymph nodes (196.6)	0 (0)	3 (1.0)
Lymph nodes of multiple sites (196.8)	0 (0)	3 (1.0)
Lymph nodes site unspecified (196.9)	1 (0.4)	8 (2.8)
Lung (197.0)	52 (18.4)	143 (49.7)
Mediastinum (197.1)	0 (0)	7 (2.4)
Pleura (197.2	0 (0)	8 (2.8)
Other respiratory organs (197.3)	0 (0)	4 (1.4)
Small intestine (197.4)	1 (0.4)	6 (2.1)
Large intestine and rectum (197.5)	0 (0)	4 (1.4)
Retroperitoneum and peritoneum (197.6)	3 (1.1)	16 (5.6)
Liver, specified as secondary (197.7)	11 (3.9)	49 (17.0)
Other digestive organs and spleen (197.8)	2 (0.7)	9 (3.1)
Other urinary organs (198.1)	1 (0.4)	5 (1.7)
Skin (198.2)	1 (0.4)	12 (4.2)
Brain and spinal cord (198.3)	6 (2.1)	32 (11.1)
Other parts of nervous system (198.4)	1 (0.4)	2 (0.7)
Bone and bone marrow (198.5)	67 (23.7)	104 (36.1)
Ovary (198.6)	1 (0.4)	0 (0)
Adrenal gland (198.7)	10 (3.5)	28 (9.7)
Genital organs (198.82)	1 (0.4)	1 (0.3)
Other (198.89)	4 (1.4)	35 (12.2)

the first 4 years after FDA approval of pazopanib for treatment of RCC using the original liver monitoring guidelines. At each interval, all cumulatively accrued patients were incorporated into the analyses; the present paper reports the findings from the final patient cohorts. Baseline characteristics were summarized as number and percentage of patients for categorical variables and mean and standard deviation (SD) for continuous variables. With the exception of time to LC elevation, each outcome of interest was reported as the denominator eligible for the analysis, the numerator (number of patients with the outcome), and the percentage of eligible patients with the outcome.

Ethical approvals/subject consent for the protection of human subjects via institutional review board or other ethical board review was obtained at the VA and PHARMO. Data obtained from the Altos database were deidentified and HIPPA compliant; thus, ethics approval was not required.

RESULTS

Patient Characteristics

A total of 283 Altos patients and 288 VA patients qualified for the analysis. Pazopanib use in the PHARMO Database Network has lagged considerably behind the US-based data sources, partly due to later drug approval in The Netherlands (February 2011). In PHARMO, 34 pazopanib users were identified, and only 4 met all inclusion criteria during the study period. Hence, this database was excluded from the analyses presented below. The mean (SD) age was 65.1 (10.6) years for Altos patients and 68.1 (8.7) for the VA cohort; 64.2% and 98.3% of patients were male in Altos and the VA, respectively (Table 1).

TABLE 2. Use of Pazopanib and Other Antineoplastic Agents in the Altos and Veterans Affairs Databases

Antineoplastic Use	Altos (n = 283) n (%)	VA (n = 288) n (%)
Line of therapy for pazopanib regimen		
First	121 (42.8)	198 (68.8)
Second	78 (27.6)	62 (21.5)
Third or higher	84 (29.7)	28 (9.7)
Previous therapies		
Sunitinib	93 (32.9)	28 (9.7)
Everolimus	63 (22.3)	31 (10.8)
Temsirolimus	44 (15.5)	17 (5.9)
Sorafenib	29 (10.2)	17 (5.9)
Bevacizumab	25 (8.8)	2 (0.7)
Denosumab	16 (5.7)	0 (0)
Axitinib	6 (2.1)	0 (0)
Bendamustine	2 (0.7)	0 (0)
Docetaxel	2 (0.7)	1 (0.3)
Doxorubicin	2 (0.7)	2 (0.7)
Rituximab	2 (0.7)	0 (0)
Capecitabine	1 (0.4)	0 (0)
Carboplatin	1 (0.4)	0 (0)
Cisplatin	1 (0.4)	0 (0)
Cyclophosphamide	1 (0.4)	0 (0)
Erlotinib	1 (0.4)	0 (0)
Gemcitabine	1 (0.4)	2 (0.7)
Ifosfamide	1 (0.4)	1 (0.3)
Imatinib	1 (0.4)	0 (0)
Methotrexate	1 (0.4)	2 (0.7)
Paclitaxel	1 (0.4)	0 (0)
Trastuzumab	1 (0.4)	0 (0)
Megestrol	0 (0)	18 (6.2)
Irinotecan	0 (0)	1 (0.3)
Temozolomide	0 (0)	1 (0.3)
Vinorelbine	0 (0)	1 (0.3)
Pazopanib prescriptions during follow-up		
No. prescriptions		
1	153 (54.1)	60 (20.8)
2	63 (22.3)	80 (27.8)
3–4	40 (14.1)	68 (23.6)
5+	27 (9.5)	81 (28.1)
Total months of use: mean (standard deviation)	4.2 (3.6)	10.3 (7.2)

TABLE 3. Prescriber Compliance to Liver Chemistry Monitoring Guidelines

Prescriber Compliance Metric*	Altos n/Total (%)	Veterans Affairs n/Total (%)
Baseline LC	209/283 (73.9)	211/288 (73.3)
LC monitoring every 4 weeks for 4 months among 4-month users with normal baseline LC	22/57 (38.6)	53/145 (36.6)
LC monitoring every 4 weeks for 4 months among all users with normal baseline LC	102/165 (61.8)	57/172 (33.1)
Weekly LC monitoring after ALT 3x-8xULN	5/9 (55.6)	14/25 (56.0)
Return to baseline or grade 1 after ALT 3x-8xULN	1/5 (20.0)	5/14 (35.7)
Pazopanib interrupted after ALT >8xULN	1/1 (100)	3/3 (100)
Pazopanib discontinued after ALT >3xULN and bilirubin >2xULN	3/3 (100)	2/2 (100)
Baseline total bilirubin ≤3x ULN	209/209 (100)	211/211 (100)

* Full eligibility criteria for each analysis are described in the text.

ALT indicates alanine aminotransferase; ULN, upper limit of normal.

Comorbidities were not reliably recorded in the Altos database; the prevalence of diabetes in the VA cohort was 42.7% (data not shown). The most common metastases in Altos and the VA, respectively, were located in the lung (18.4%, 49.5%) and bone and bone marrow (23.7%, 36.0%). The presence of liver metastases was recorded among 3.9% of Altos patients and 17.0% of VA patients (Table 1).

Pazopanib was used as first-line therapy for 42.8% of Altos patients and 68.8% of VA patients (Table 2). Previous antineoplastic treatments in the Altos and VA cohorts, respectively, included sunitinib (32.9%, 9.7%), everolimus (22.3%, 10.8%), temsirolimus (15.5%, 5.9%), sorafenib (10.2%, 5.9%), and bevacizumab (8.8%, 0.7%). The mean (SD) duration of pazopanib treatment was 4.2 (3.6) months in Altos and 10.3 (7.2) months in the VA.

Prescriber Compliance

Of the qualifying cohort of 283 pazopanib initiators in the Altos database, 73.9% received baseline LCs (Table 3). The corresponding percentage in the VA database was 73.3%. Among the 57 Altos patients with at least 18 weeks of continuous pazopanib exposure and normal ALT and bilirubin at baseline, 38.6% had LC tests administered every 4 weeks for the first 4 months. Of the 145 VA patients qualifying for this analysis, 36.6% had evidence of LC monitoring every 4 weeks for the first 4 months. In both databases, LC monitoring was more frequent in the first month of drug use than in later months. In the Altos cohort, the percentage of patients with LC measurements declined from 78.9% in month 1 (excluding days 1–13) to 73.7% in month 2 to 59.6% in month 3 to 54.4% in month 4 (Fig. 1). The VA patients showed LC monitoring in months 1 to 4, respectively, for 86.2%, 68.3%, 66.2%, and 64.8% of patients (Fig. 2).

The number of eligible patients greatly increased, especially Altos, in the analysis of LC monitoring among all patients initiating pazopanib who had normal baseline ALT and bilirubin (ie, including those with less than 18 weeks of pazopanib exposure). Of 165 qualifying patients from Altos, LC monitoring every 4 weeks for the duration of pazopanib use (up to 4 months) was observed for 61.8% of patients. In the VA, 33.1% of 172 patients had LC monitoring every 4 weeks.

Nine pazopanib users in Altos had isolated ALT elevations between 3x and 8xULN, of whom, 5 patients (55.6%) underwent appropriate weekly monitoring; 20.0% reverted to baseline or grade 1 among the 5 persons tested. The VA cohort included 25 patients with an ALT elevation meeting these criteria; 14 patients (56.0%) received weekly LC monitoring, and 35.7% of the 14 patients monitored showed a return to baseline or grade 1 levels. One Altos patient and 3 VA patients had an isolated ALT elevation greater than 8xULN; all of these patients discontinued the drug after the ALT elevation (100%).

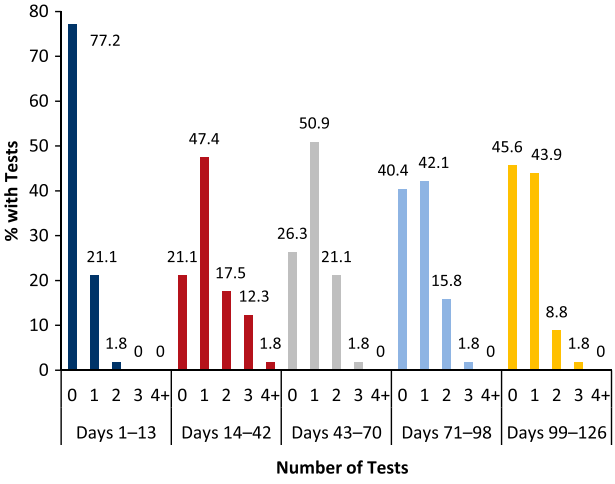

FIGURE 1. The number of alanine aminotransferase (ALT) and bilirubin tests during the first 4 months of pazopanib use in the Altos database. Includes only patients with 18 weeks or greater of continuous pazopanib exposure.

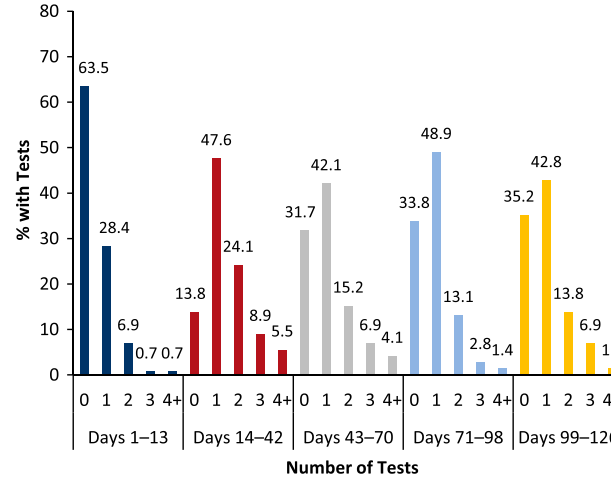

FIGURE 2. The number of alanine aminotransferase (ALT) and bilirubin tests during the first 4 months of pazopanib use in the Veterans Affairs database. Includes only patients with 18 weeks or greater of continuous pazopanib exposure.

Three pazopanib initiators in Altos and 2 in the VA had concurrent ALT and bilirubin elevations (ALT >3xULN and bilirubin >2xULN), all of whom discontinued pazopanib after the elevation (100%). No pazopanib initiators (0%) in either Altos or the VA were found to have baseline preexisting severe hepatic impairment, defined as total bilirubin greater than 3xULN, at the time of pazopanib start.

DISCUSSION

Results from the Altos and VA databases indicate that LC monitoring by prescribers is not optimal, with 73% to 74% compliance for baseline testing and 37% to 39% compliance with testing every 4 weeks for the first 4 months among those with at least 4 months of pazopanib use. Compliance with monitoring guidelines was greatest shortly after drug initiation and decreased over time (in Altos, compliance declined from 79% to 54% from month 1 to month 4, and in the VA from 86% to 65%). Among patients who should have had weekly testing, the compliance was 56% in both databases. The more serious liver enzyme elevations examined, including ALT over 8xULN and concurrent ALT greater than 3xULN and bilirubin greater than 2xULN, were infrequent but always led to appropriate discontinuation of pazopanib.

Compliance with LC monitoring guidelines for drugs other than pazopanib has shown considerable variability in previous studies. A study using Medicaid data on troglitazone prescribing, before its withdrawal from the US market in 2000 prompted by liver failure events, found that 18.6% of patients received liver enzyme testing before drug initiation, 6.4% received a follow-up test during the first 4 weeks of use, and 51.6% had at least one test within six months of drug start, despite recommendations of monthly testing during troglitazone exposure.[6] This highly publicized failure to prevent serious liver outcomes through adequate monitoring may have helped to increase awareness among physicians prescribing other treatments requiring liver monitoring, as studies conducted in later years, including the present analysis, have typically produced higher compliance estimates. For example, LC monitoring at baseline with isoniazid was found in 75.0% of patients and during follow-up in 74.8% of drug episodes requiring monitoring[7]; note that the unit of analysis was the drug episode rather than the patient, so the follow-up results cannot be compared directly with the present findings. A study examining many drugs with black box warnings investigated compliance at the patient level, with baseline and follow-up monitoring combined; compliance ranged from 17.3% for weekly monitoring of LCs during ketoconazole use, to 49.3% for monitoring every 4 months with anabolic corticosteroids, to 69.9% for yearly monitoring with valproate sodium.[8] Considering that pazopanib requires monthly monitoring of LCs, the present findings appear to be consistent with these patient-level results.

Safety guidelines for drug prescribing are communicated not only through black box warnings and product labeling but also via direct health-care professional communications and public health advisories. Research into the effectiveness of these approaches has produced varying results but suggests that clear, concise, and specific wording may play an important role in improving compliance.[7,9–11] Tailored approaches including timely feedback to prescribers who violate guidelines may be particularly effective.[12] However, it is possible that noncompliance may be due in some instances to clinicians choosing to limit the number of blood draws for LC control in critically ill patients or patients not getting lab work completed as directed by their physician.

Strengths of the study include the use of 2 large databases containing information on both prescription drugs and laboratory tests with results, allowing for a real-world examination of prescriber compliance. Despite the differences between the 2 databases and their source populations, the findings are generally consistent from each, suggesting good validity of the analyses within each database. The sequential analyses at semiannual intervals allowed for ongoing assessment as pazopanib uptake progressed in the United States, rather than waiting through 4 years of patient accrual before conducting the analysis. This sequential approach allowed timely reporting to the regulatory agencies monitoring the safety profile of pazopanib in ongoing clinical practice.

LIMITATIONS

To investigate prescriber compliance with guidelines, a retrospective observational study design is best, as active participation in a study may influence prescribing and monitoring behaviors. Yet the design and the data sources carry important limitations. Any laboratory tests that occurred outside the EMR systems contributing data did not appear in the analysis, which may lead to underestimation of compliance. Exposure time to pazopanib was estimated based on prescription data for the Altos cohort and pharmacy dispensing data for the VA cohort. The actual timing of drug exposure may have differed from the coded exposure time, which can have 2 opposing effects. First, if pazopanib was not in use during periods of prescription/dispensing supply, then compliance may have been underestimated as liver monitoring was not needed. On the other hand, if pazopanib was in use during periods of apparent nonuse, compliance may have been underestimated. Also, in the Altos database, it is difficult to identify new users, as prescriptions could have been obtained outside the EMR system, and a lengthy baseline clean period before the first pazopanib prescription was not feasibly to apply, given that many patients begin treatment shortly after the start of care in the oncology practice. Continuing users of pazopanib would not have required the frequent LC monitoring that is mandated for new users. Generalizability of the populations of these databases is also limited, especially for the VA, whose population is composed primarily of male veterans with a median age of 65. A European population was not able to be studied because of year lag time before the approval of pazopanib by the EMA.

CONCLUSIONS

This population-based study showed that liver monitoring compliance among prescribers was reasonable near pazopanib initiation but very low during subsequent weeks of treatment.

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